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Diastereoselective Total Synthesis of (±)-Codeine

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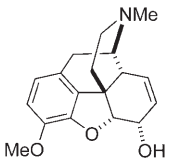
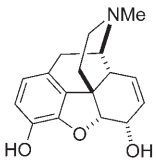
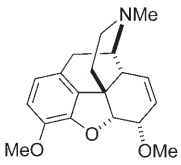
Codeine **1** and morphine **2**, the principal constituents of opium, continue to attract the attention of organic chemists thanks to both their biological activities and their unique structure.[1] Their complex pentacyclic skeleton, which includes a quaternary carbon center, has stimulated extensive efforts. To date there have been more than 20 total syntheses of codeine (**1**), morphine (**2**), and thebaine (**3**).[2] We were interested in the synthesis of codeine for two reasons: first, codeine was found to be an allosteric potentiating ligand of nicotinic receptors,[3] and second we have a general program underway in the laboratory in which we have shown that tricyclic spirocyclohexadienones are valuable intermediates for the synthesis of natural products in the *Amaryllidacea* galanthamine-type, maritidine-type, and *Aspidosperma* alkaloids.[4]



1 (-)-Codeine



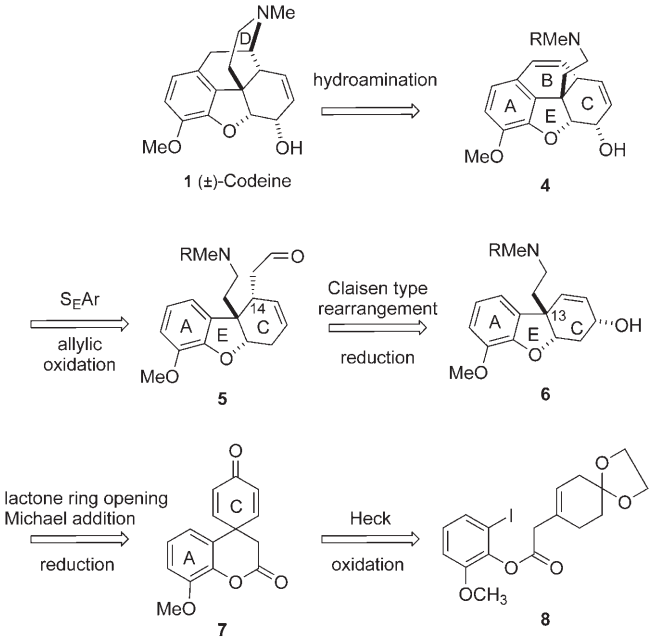
2 (-)-Morphine



3 (-)-Thebaine

In an effort to develop new allosteric potentiating ligands of nicotinic receptors with a codeine-type scaffold, we initiated our own studies of a total synthesis of codeine. Herein we disclose a total diastereoselective synthesis of (±)-codeine (**1**), which involves a new construction of the morphinan skeleton. The present study provides an efficient method for the elaboration of the quaternary carbon at C-13 and for the highly diastereoselective introduction of the C-14 stereogenic center of the morphinan system.

Our retrosynthetic analysis of (±)-codeine (**1**) is shown in Scheme 1. Codeine could be obtained from amine intermediate **4** by using an intramolecular hydroamination reaction to form the D ring. Compound **4** could in turn be prepared from aldehyde **5**. In our synthetic pathway, we planned to use for the first time a Claisen-type rearrangement to introduce the C-14 substituent. This type of rearrangement applied to compound **6** would provide a precursor of the aldehyde **5** and control the stereochemistry of the substituent at C-14 of **5**. The tricyclic amine **6** would be obtained from the spirocyclohexadienone **7** by a lactone ring opening with an amine followed by a spontaneous intramolecular Michael



Scheme 1. Retrosynthesis of (±)-codeine **1**.

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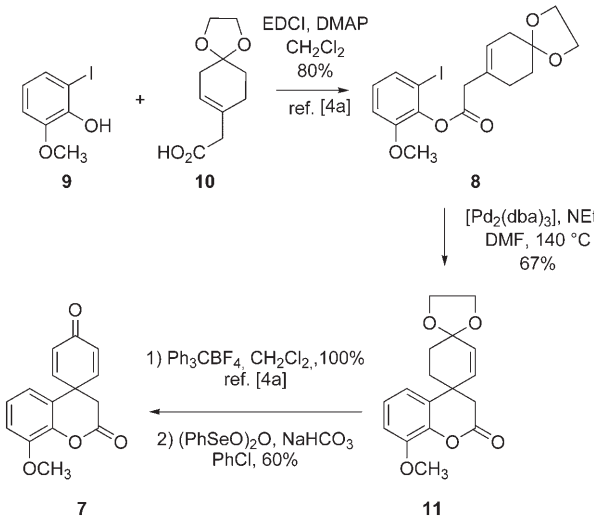
addition of the resulting phenol to cyclohexadienone. Compound **7** could be prepared in two steps from the ester **8** by an intramolecular Heck reaction followed by an oxidation.

Our synthesis started with esterification of 2-iodo-6-methoxyphenol (**9**)[5] with acid **10**[6] according to a known procedure.[4a] Heck cyclization of **8** was accomplished in 67% yield under new conditions. Indeed, in the absence of phosphine ligands, the reaction time for the cyclization of **8** to **11** was greatly reduced from three days[4a] to 5 h.[7] After hydrolysis of the dioxolane group of **11** with triphenylcarbenium tetrafluoroborate,[4a] oxidation of the α,β-unsaturated ketone function of the resulting product to the corresponding dienone **7**[4a] was realized in the presence of $(PhSeO)_2O$ and $NaHCO_3$ (Scheme 2).

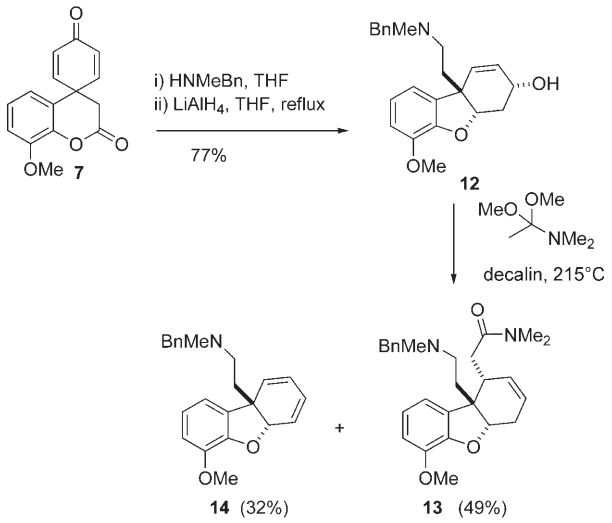


Scheme 2. Synthesis of tricyclic spirocyclohexadienone **7**. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMAP = 4-dimethylaminopyridine, dba = dibenzylideneacetone.

The reaction of lactone **7** with *N*-methylbenzylamine with concurrent amide formation and lactone ring opening afforded the corresponding enone, which was then reduced with $LiAlH_4$ to give the allylic alcohol **12** in 77% yield (Scheme 3). With a ready access to the key tricyclic allylic alcohol **12**, we then turned our attention to the introduction of the crucial substituent at C-14.

Several approaches have been developed to introduce this substituent based on the intramolecular Heck reaction,[2a,e,8] the tandem radical cyclization,[9] 1,4-addition of vinyl magnesium bromide (in the presence of copper(I) bromide) to α,β-enone,[10] CpCO-mediated [2+2+2] cyclization of functionalized 4-(3-butynyl)benzofurans,[11] or by aldol condensation.[2c]

In our study, introduction of the C-14 substituent starting from allylic alcohol **12** proved difficult. Attempts to achieve a Claisen rearrangement on **12** under Kazmaier's,[12] Ireland's,[13] or Johnson's[14] conditions failed.

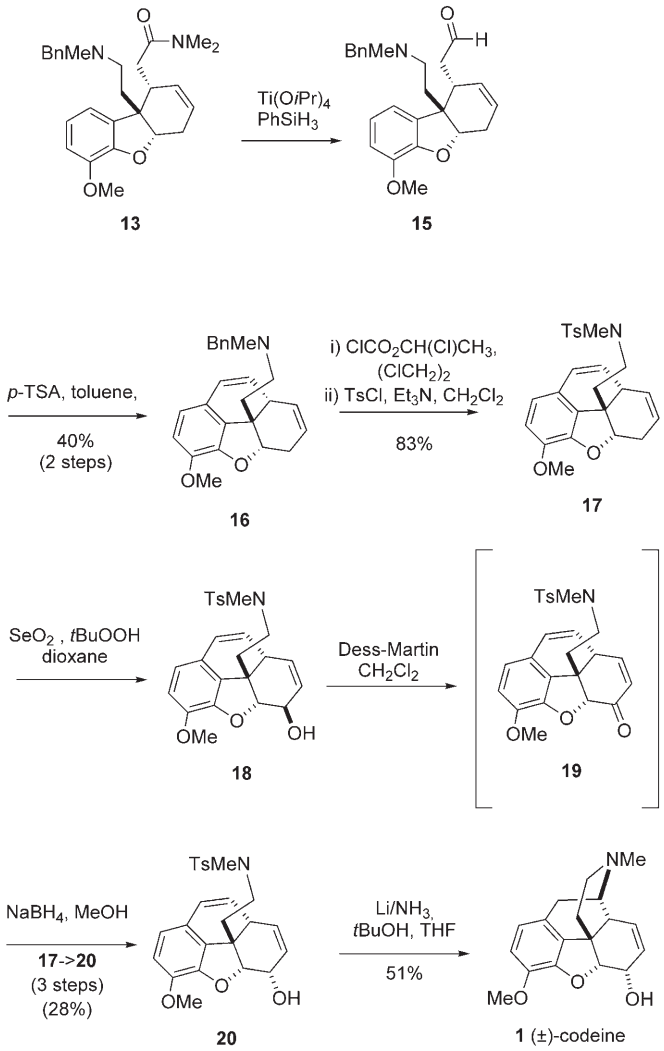


Scheme 3. Synthesis of amide **13**.

However, we found that, under Eschenmoser's[15] conditions, the C-14 substituent could be diastereoselectively introduced. Heating **12** in the presence of dimethylacetamide dimethylacetal in decalin at 215 °C afforded the expected amide **13** (49%) and diene **14** (32%) as a by-product (Scheme 3). In spite of numerous attemps,[16] it was not possible to reduce the amount of **14** produced.

Reduction of the amide **13** with $PhSiH_3$ in the presence of $Ti(OiPr)_4$[17] yielded the aldehyde **15**, which upon treatment with *p*-TSA in toluene furnished the amine **16** (Scheme 4). The next step was the introduction of the allylic alcohol function. To prevent oxidation of the nitrogen atom, the *N*-benzyl group was first removed in the presence of 1-chloroethyl chloroformate to give the corresponding secondary amine, which was then protected with TsCl to give the sulfonamide **17**. Oxidation of **17** with SeO_2 in presence of *t*BuOOH in dioxane furnished the allylic alcohol **18** with incorrect stereochemistry. The latter was thus oxidized into the corresponding ketone **19** by reaction with Dess–Martin periodinane. Reduction of ketone **19** proceeded stereoselectively using $NaBH_4$ in methanol to give the required alcohol **20** now having the correct stereochemistry. The final step required to construct the D ring of codeine involves a hydroamination reaction. This type of cyclization was recently applied to a precursor of codeine (using $Hg(OAc)_2$ and then $LiAlH_4$) to give (+)-codeine in 17.6% yield.[2d] In our case, we found that exposure of the sulfonamide **20** to lithium in liquid ammonia[18] resulted in reductive cyclization to furnish codeine (**1**) in satisfactory yield (51%).

In conclusion, we have achieved a diastereocontrolled synthesis of (±)-codeine (**1**) from the tricyclic spirocyclohexadienone **7** in 10 steps. An intramolecular Heck reaction followed by a Claisen–Eschenmoser rearrangement, a reductive deprotection, and an intramolecular hydroamination reaction constitute the key steps of this new total synthesis of codeine.



Scheme 4. Synthesis of (±)-codeine **1**. *p*-TSA = *p*-toluenesulfonic acid.

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Keywords: alkaloids · diastereoselectivity · Heck reaction · hydroamination · rearrangement · total synthesis

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